Increased Risk of Cerebral Palsy in IVF/ICSI Babies: Meta analysis of Current Literature

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Abstract

Background:

The correlation between assisted reproductive therapies (ARTs) and congenital or developmental anomalies has been acknowledged by prominent obstetric and reproductive science authorities. However, the orthopedic perspective on this aspect of ARTs remains largely unexplored. This meta-analysis aims to examine a plausible association between cerebral palsy and in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) therapies within the realm of assisted reproductive technologies (ARTs).

Methods:

The literature spanning from 1980 to February 2024 was systematically reviewed within the MEDLINE, Scopus, and Embase databases, adhering to the PRISMA guidelines. Data synthesis was conducted using the Jamovi program.

Results:

The literature review involved an initial search that yielded 192 articles, which were subsequently refined to 21 articles following the removal of duplicates and screening for relevance. These articles, selected according to the PRISMA model, collectively included data from 8,657,973 patients. Upon analyzing the dataset, it was found that among 8,400,080 control patients, there were 14,518 cases of cerebral palsy, while among 237,873 patients who underwent IVF or ICSI, 736 cases of cerebral palsy were documented. This analysis revealed that the incidence of cerebral palsy was approximately 1.9 times higher in IVF and ICSI cases compared to control groups (p < 0.001, adjusted odds ratio = 1.9, 95% confidence interval: 1.570–2.323).

Conclusion

As a result, the risk of developing cerebral palsy, as in many other congenital anomalies and pediatric diseases, in babies born with assisted reproductive techniques is statistically significantly higher than in normal babies. This, together with the sensitive monitoring of the neonatal period and perinatal period in women conceived with ART. It is recommended that teams collaborate with pediatric orthopedic surgeons.

Introduction

In vitro fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI) have revolutionized the field of reproductive medicine, enabling millions of individuals and couples to overcome infertility and start families (1,2). While IVF and ICSI significantly increase pregnancy success, they also raise important
ethical and medical issues, particularly regarding the potential for congenital anomalies in children born via IVF/ICSI (3–5).

Congenital anomalies, also known as birth defects, are structural or functional abnormalities that are present at birth. They can range from minor cosmetic issues to serious or life-threatening conditions that require significant medical attention (3–5). The causes of congenital anomalies are complex and multifactorial, including genetic, environmental, and random factors. Over the years, extensive research has been conducted to understand the relationship between in vitro fertilization and congenital anomalies (3–5). Several studies suggest that the prevalence of certain congenital anomalies is higher in children born via IVF/ICSI compared to children born naturally (3–5).

However, this situation has not been comprehensively investigated specifically in orthopedic problems or cerebral palsy, which are the most common congenital or prematurity-related problems. In this study, we comprehensively discussed the relationship between cerebral palsy and ICSI/IVF.

## Methods

### 2.1 Study Designing

This study was designed as a meta-analysis, spanning 44 years of literature from 1980 to 2024. The primary endpoint of this study was to determine the difference in the incidence of cerebral palsy between natural conception and IVF/ICSI.

### 2.2 Search Strategy and Study Criteria

The search methodology involved querying the PUBMED and Scopus databases using two distinct search strategies: (1) (IVF) AND (Cerebral Palsy) and (2) (ICSI) AND (Cerebral Palsy).

Studies meeting the following inclusion criteria were considered: (1) inclusion of either IVF or ICSI groups, (2) presence of a control group for comparison, (3) provision of the total number (n) of "AT LEAST ONE" of the cp case in both the IVF/ICSI groups and the control group, (4) publication in English, and (5) inclusion of at least 10 patients in each group.

Exclusion criteria encompassed reviews, meta-analyses, case series, and case reports, with a focus solely on original research articles that met the criteria for comprehensive analysis.

During this selection process we followed PRISMA guideline(6).

### 2.3 Data Extraction

Relevant data, including bibliographic details such as publication year and author surname, were extracted from each publication selected based on detailed criteria. Additionally, information regarding the total cohort size and the number of patients affected by cerebral palsy was meticulously documented.
2.4 Endpoint definition

Data analysis was structured into two principal stages. In the pre-processing phase, meticulous examination of the data was conducted to ascertain the patient count within both the control and assisted reproductive technology (ART) groups. Following this, the occurrence of cerebral palsy within each group was meticulously documented. The primary emphasis during analysis was placed on calculating the percentage of patients afflicted with cerebral palsy within the respective groups.

2.5 Data Synthesis

The synthesis of data was meticulously carried out by two seasoned academics proficient in statistics and epidemiology. Given the extensive number of patients expected to be included and the likelihood of encountering low study quality and missing patient data, the anticipated heterogeneity of results was carefully considered. However, despite these challenges, the results were presented per study alongside their corresponding 95% confidence intervals (95% CIs) to effectively illustrate the incidence of cerebral palsy in assisted reproductive technologies (ARTs). Each study was meticulously weighted based on sample size and data distribution, ensuring an accurate representation of the rates observed. These aggregated rates were subsequently combined and consistently reported. To evaluate the degree of heterogeneity among the studies, the I² statistic was employed, with values exceeding 50% and their corresponding P-values indicating significant heterogeneity. The synthesis process utilized Jamovi, a freely available software program, to ensure robust analysis and interpretation of the data(7).

Results

3.1 literature

A thorough search utilizing pertinent keywords yielded a total of 192 articles from the designated database systems. Following the removal of duplicates and screening for relevance based on titles, the analysis narrowed down to 76 abstracts, resulting in the exclusion of 50 articles. The final filtration process, conducted in accordance with the PRISMA model, ultimately included 21 articles for detailed analysis(8-28). These selected articles collectively encompassed data from 8,657,973 patients. For a comprehensive overview of the study selection process, please refer to Figure 1 and Table 1.

3.2 Comparison between ARTs and Control

After conducting a comprehensive analysis of the dataset, it was observed that among 8,400,080 control patients, 14,518 cases of cerebral palsy were identified. In contrast, among 237,873 patients who underwent either in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), 736 cases of cerebral palsy were documented. Upon meticulous data synthesis, it became evident that the incidence of cerebral palsy was approximately 1.9 times higher in IVF and ICSI cases compared to other control groups. (p<0.001,95% confidence interval: 1.570-2.323) (figure 2 and figure 3).

3.3 Heterogeneity of the literature
Following heterogeneity analysis, the I² statistic was calculated to be 73.5%, which indicates a moderate to high level of heterogeneity among the studies included in the analysis. This suggests that there is a considerable amount of variability in the study results beyond what would be expected by chance alone. The p-value associated with this finding is less than 0.001, indicating that the observed heterogeneity is statistically significant. Additionally, the tau² value, a measure of between-study variance, was calculated to be 0.1125. This further supports the presence of heterogeneity among the studies, as a tau² value greater than zero suggests that the true effect size may vary across studies.

**Discussion**

As infertility rates and maternal ages continue to rise, the utilization of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) is steadily increasing (2). These assisted reproductive technologies (ART) have a well-established track record of success in helping couples conceive. (1-2) However, the topic of concern regarding the prevalence of congenital anomalies in pregnancies resulting from IVF and ICSI has been a topic of ongoing debate within the medical community (1-5). Potential hypotheses behind this phenomenon include factors such as maternal age at the time of IVF/ICSI, multiparity, and innate susceptibility to natural congenital pathologies (29-30). Some causes of female infertility can predispose embryos to malformations and increase the risk of prematurity (30-31). Moreover, the risk of prematurity is heightened by multiparity, which is more prevalent in IVF/ICSI cases (28-31). There are also more speculative theories, such as the potential for DNA damage during in vitro fertilization or intracytoplasmic injection (32). While meta-analyses have investigated the association between IVF/ICSI and pediatric problems such as chromosomal anomalies and congenital heart diseases, a comprehensive perspective on congenital orthopedic problems and musculoskeletal diseases has not yet been presented(3,5). Our study represents the most thorough examination of this topic to date.

In the study, we meticulously searched two vital databases and sifted through over 100,000 studies on ICSI and IVF. Surprisingly, only 192 studies addressed cerebral palsy. However, after removing duplicates and applying stringent selection criteria, only 21 publications were deemed suitable for inclusion in our analysis (8-28). This limited literature pool is characterized by moderate to high levels of heterogeneity. Notably, studies like those by Norman et al and Kallen et al, involving more than 2 million individuals, as well as studies such as Kuiper et al and Ramoglu et al, which include only a few hundred individuals, exemplify this qualitative heterogeneity. This disparity underscores the untouched nature of this area, emphasizing the necessity for further evidence and the establishment of a consensus within the field.

The most striking revelation of this study is that the likelihood of cerebral palsy after IVF/ICSI is 1.9 times higher than after natural conception. This finding underscores the comparable risk of cerebral palsy associated with IVF/ICSI to that of congenital heart diseases or chromosomal anomalies. It is imperative to investigate whether this observed relationship extends to other musculoskeletal and orthopedic problems as well.
Conclusion

The findings of this study shed light on the possible association between IVF/ICSI and an increased risk of cerebral palsy. Although the literature pool is limited, the significant increase in the likelihood of cerebral palsy after IVF/ICSI compared to natural conception warrants further exploration. Future studies should aim to elucidate the underlying mechanisms and explore potential interventions to mitigate this risk. It is also essential to investigate whether this observed relationship extends to other musculoskeletal and orthopedic problems, as this can inform clinical decision-making and patient counseling.

References


Table

Table 1:
<table>
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<th>Procedure</th>
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Figures
Figure 1

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Figure 2

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Figure 3

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